Task Force sulla patologia diabetica: LA DISLIPIDEMIA

Marco Cianciullo
Ambulatorio per la diagnosi e la terapia delle iperlipidemie – P.O. Pagani

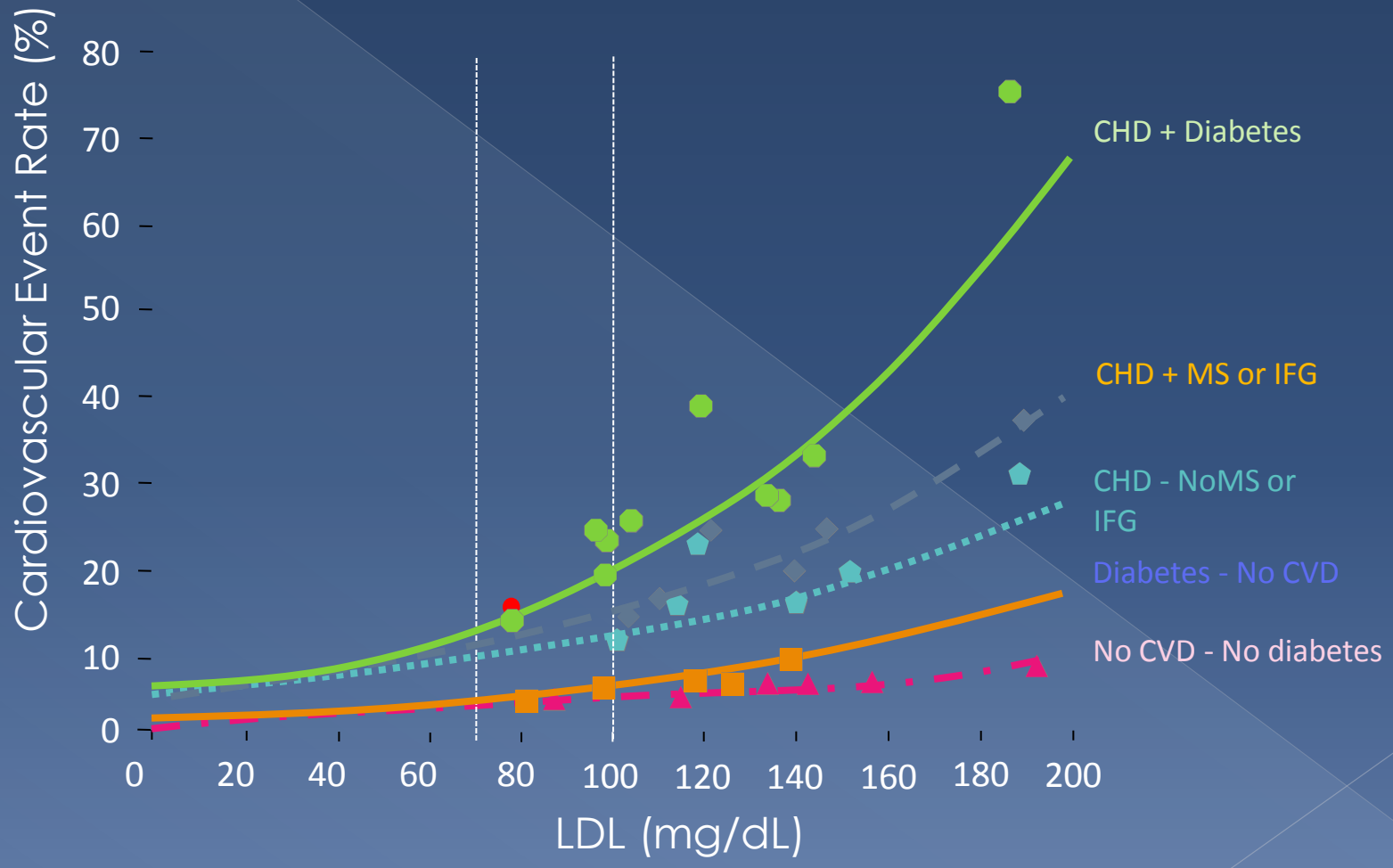
Sorrento, 21 e 22 ottobre 2011

Proverò a rispondere a 3 quesiti:

- Trattare con statine i diabetici è più conveniente?
- Utilità degli altri farmaci ipolipidemizzanti
- Le statine aumentano il rischio di diabete?

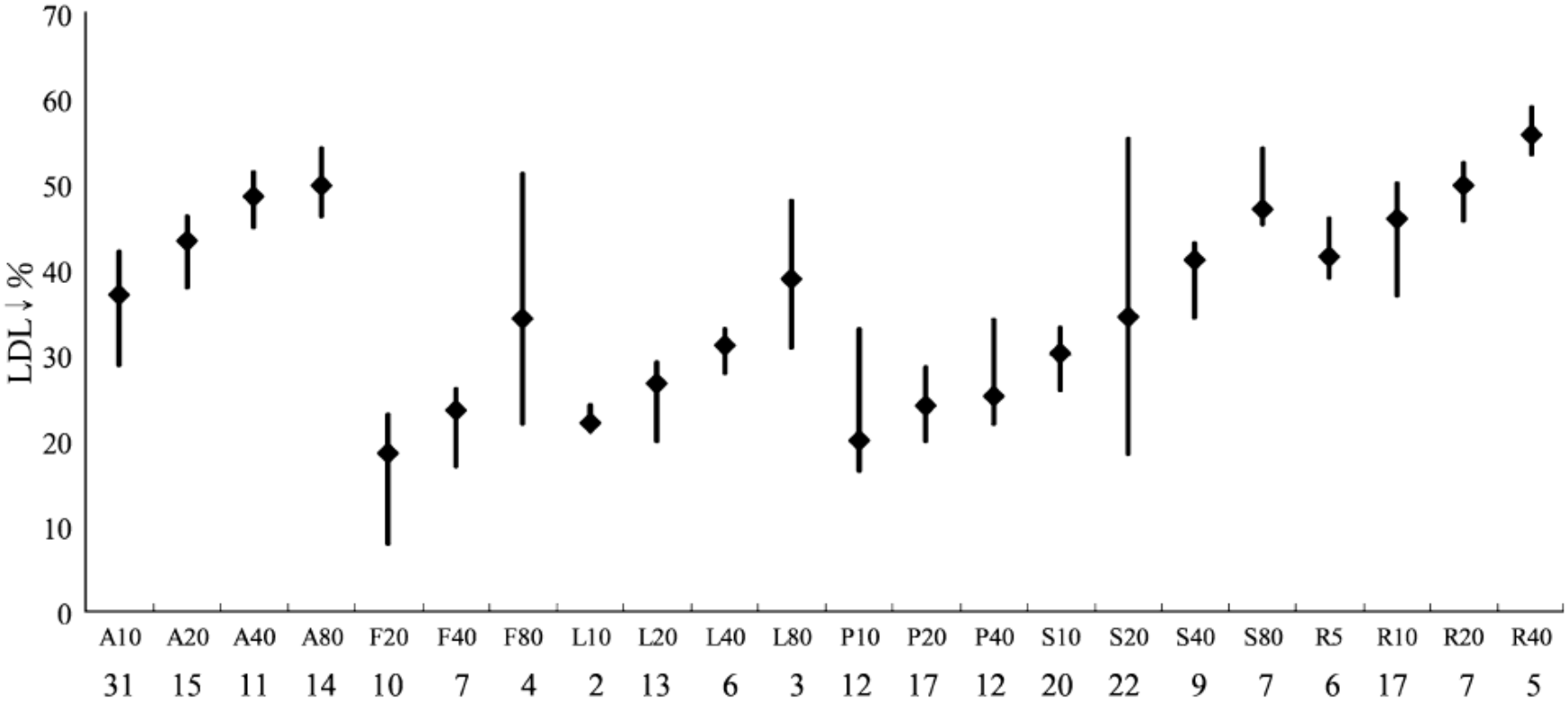
In una data popolazione, goals più bassi riducono ulteriormente gli eventi CV? *Risk Curve Concept*

Pazienti a rischio più elevato hanno più da guadagnare da una terapia aggressiva



Robinson JG, Stone NJ. Am J Cardiol. 2006;98:1405-1408

Comparisons of the lipid lowering effect of different statins: LDL



→. Comparisons of the lipid lowering effect of different statins. (1) The point estimate indicates the weighted-average of pooled analysis, and the vertical bar shows the range of lipid-lowering effects of the included studies. (2) The horizontal axis is composed of drug labels, indicating the specific statin and dose studied. A, F, L, P, S, and R stand for atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin, respectively, whereas the number after the single alphabet represents the dose used. For examples, A10 is atorvastatin 10 mg and S20 is simvastatin 20 mg. Under each drug label is the number of head-to-head comparisons involving the specific dose and statin. To illustrate, the first panel [low-density lipoprotein (LDL)-lowering effect] shows that 31 clinical trials with atorvastatin 10 mg reported the drug could reduce LDL by 28·9–42.

Weng TC, et al. J Clin Pharm Ther 2010;35:139-51

Riduzione degli eventi a 10 anni con statine in pazienti con diabete: La riduzione degli eventi correla col rischio relativo – more risk, more benefit

Endpoint: 10-year Fatal CHD/Non-fatal MI and LDL lowering NNT: 3-50

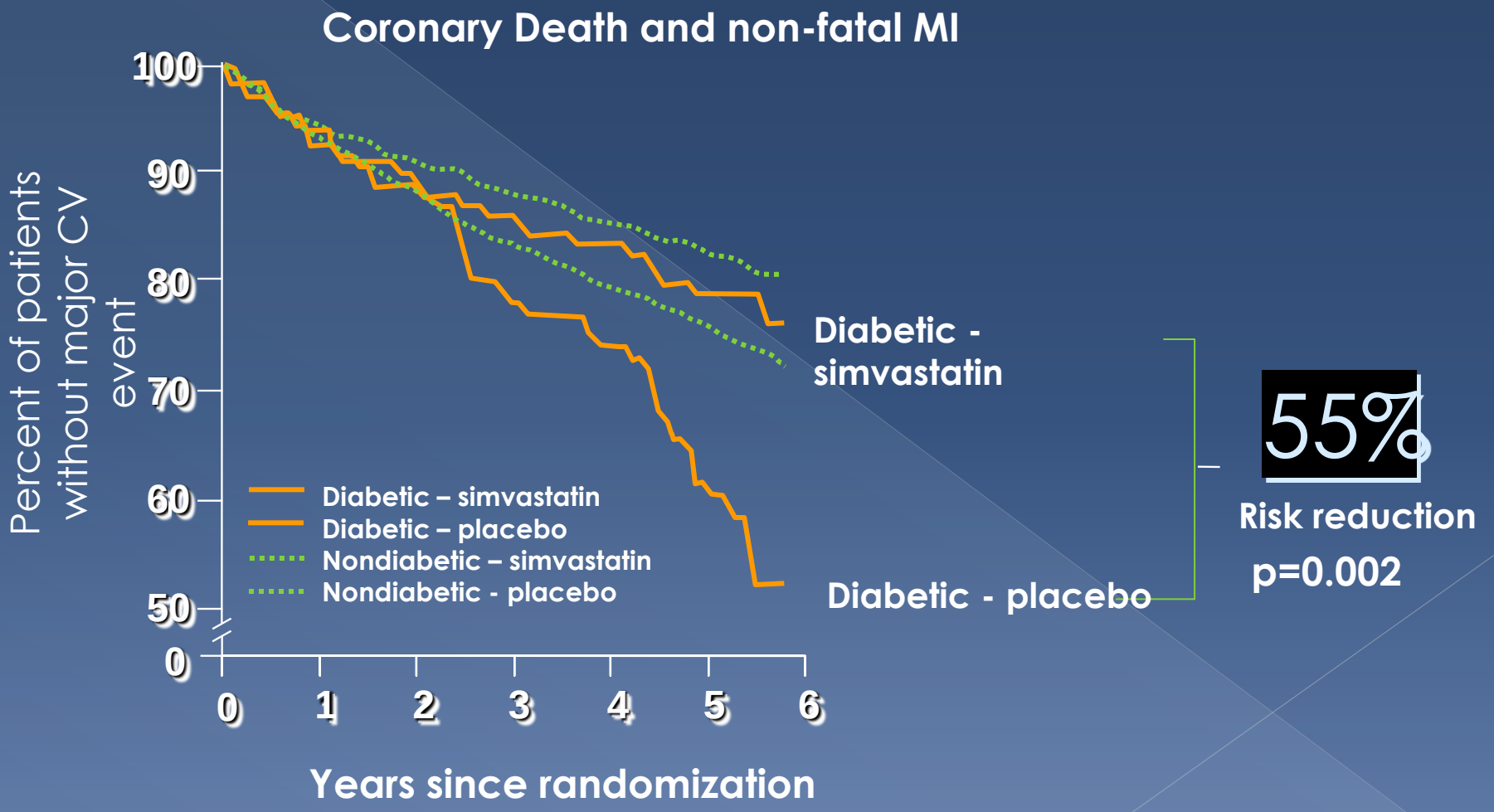
	Relative Risk reduction	ARR	LDL reduction
4S-DM	85.7 to 43.2% (50%)	42.5%	186 to 119 mg/dL (36%)
ASPEN 2^0	35.1 to 23.2% (34%)	11.9%	112 to 79 mg/dL (29%)
HPS-DM 2^0	43.8 to 36.3% (17%)	7.5%	123 to 84 mg/dL (31%)
CARE-DM	40.8 to 35.4% (13%)	5.4%	136 to 99 mg/dL (27%)
TNT-DM	26.3 to 21.6% (18%)	4.7%	99 to 77 mg/dL (22%)
HPS-DM 1^0	17.5 to 11.5% (34%)	6.0%	124 to 86 mg/dL (31%)
CARDS	11.5 to 7.5% (35%)	4%	118 to 71 mg/dL (40%)
ASCOT-DM	11.1 to 10.2% (8%)	0.9%	125 to 82 mg/dL (34%)
ASPEN 1^0	9.8 to 7.9% (19%)	1.9%	114 to 80 mg/dL (30%)

2

1

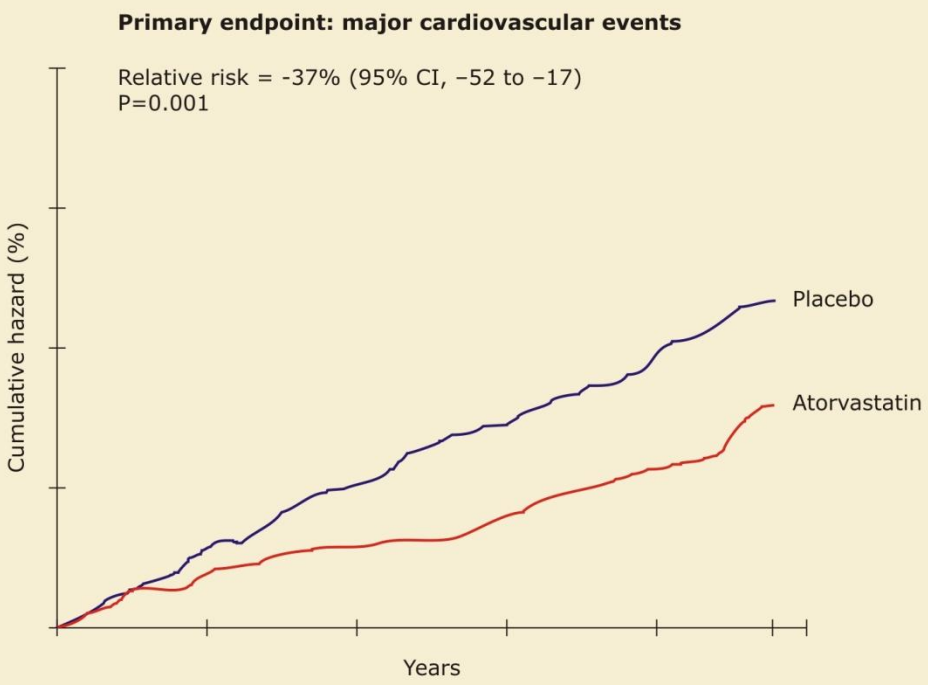
1: Primary prevention data 2: Secondary prevention
ADA STANDARDS OF CARE, Diabetes Care jan 2011

The differential benefit of LDLc lowering in patients with diabetes has been evident from the earliest statin trials and is more evidence that higher risk=greater benefit : 4S study: Major Coronary Events



Pyörälä K, et al. *Diabetes Care*. 1997;20:614–620

CARDS: The Collaborative Atorvastatin Diabetes Study
- RESULTS continued -

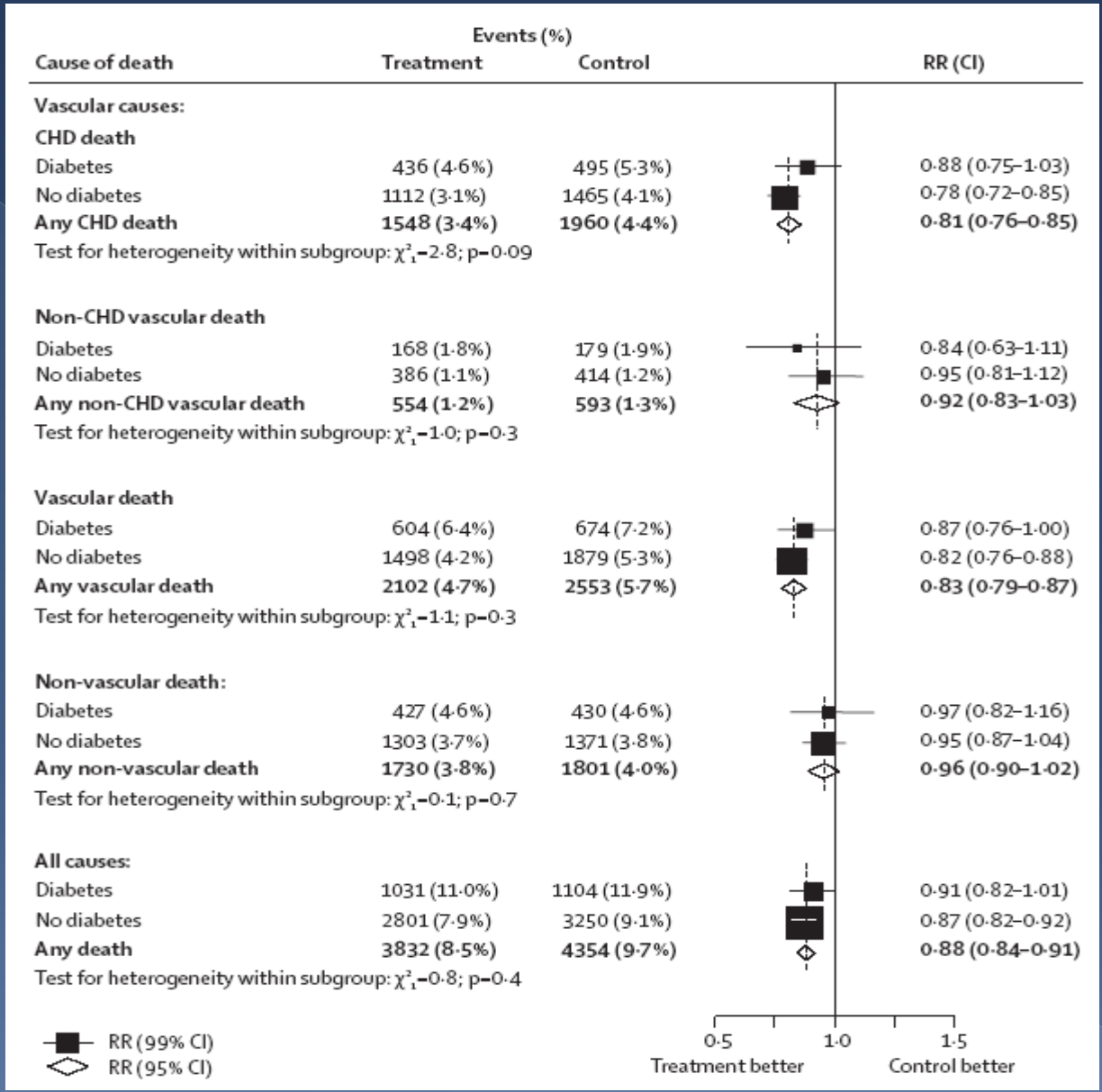


Reproduced with permission from: *N Eng J Med* 2005; 352:225–237

Efficacy of cholesterol-lowering therapy in 18 686 people with diabetes in 14 randomised trials of statins: a meta-analysis

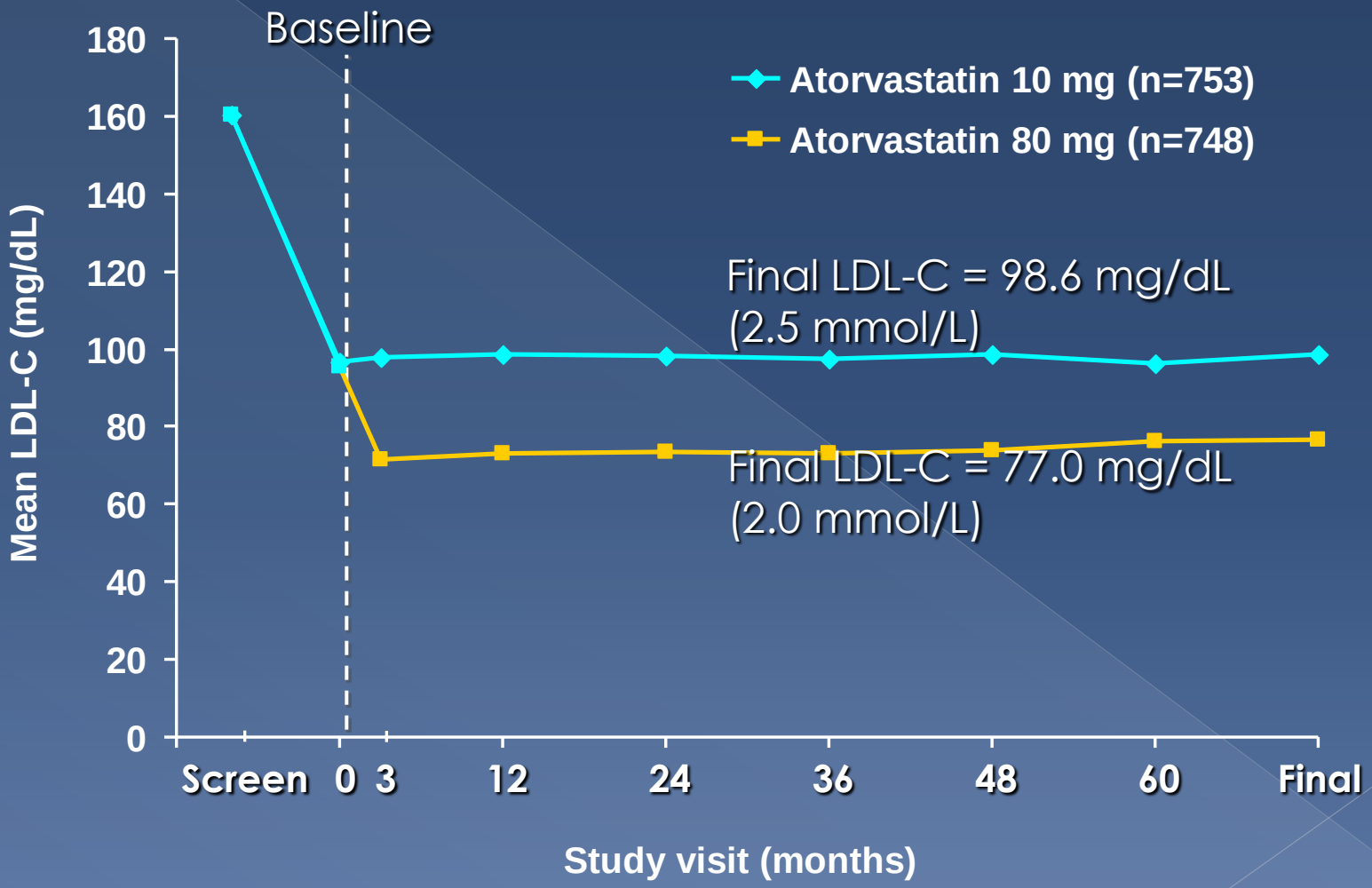
*Cholesterol Treatment Trialists' (CTT) Collaborators**

CTT Collaborators, Lancet 2008; 371: 117-125



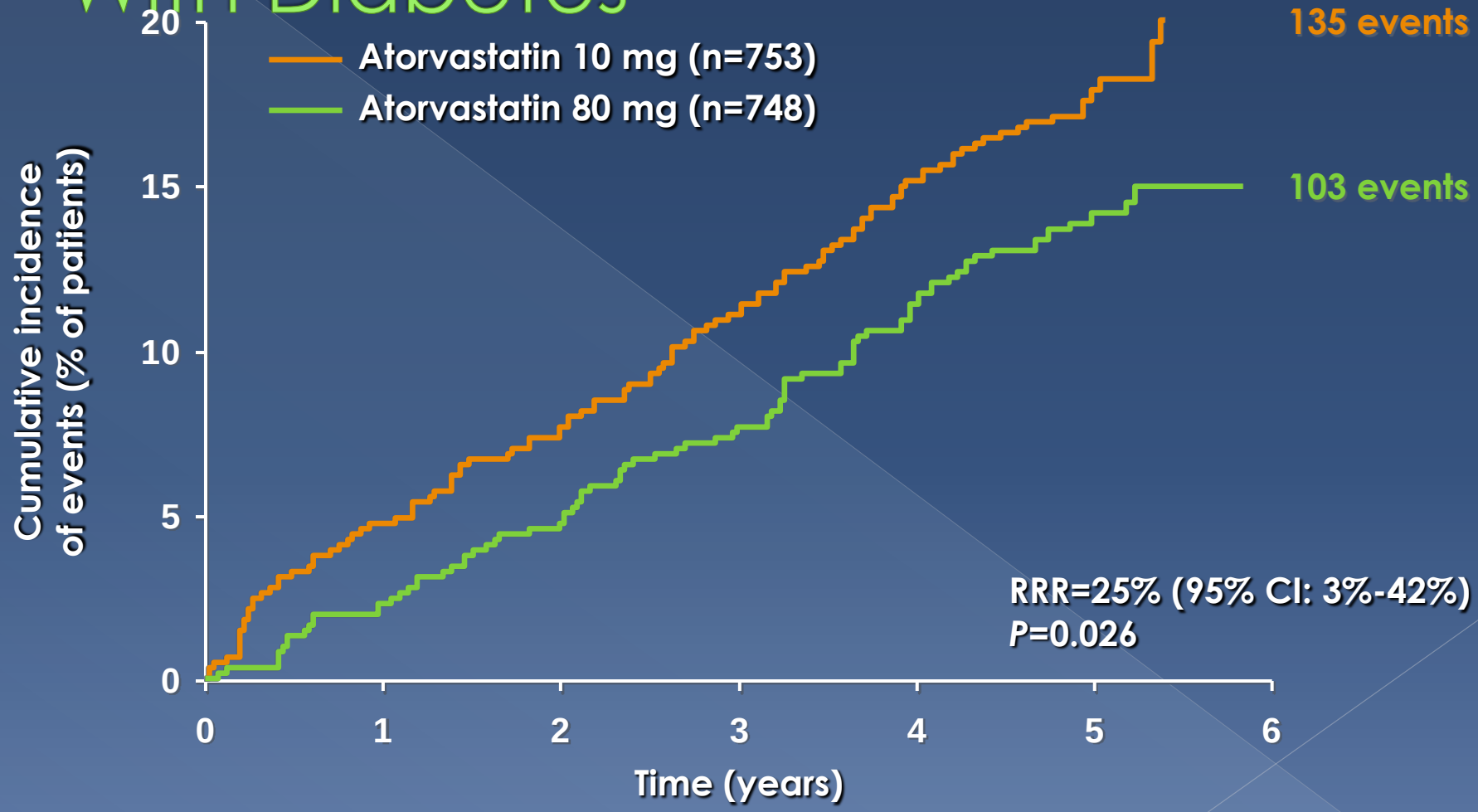
CTT Collaborators, Lancet 2008; 371: 117-125

TNT: Changes in LDL-C By Treatment Group in Patients With Diabetes



Shepherd J et al. *Diabetes Care*. 2006;29:1220-1226.

TNT: Time to First Major Cardiovascular Event* in Patients With Diabetes



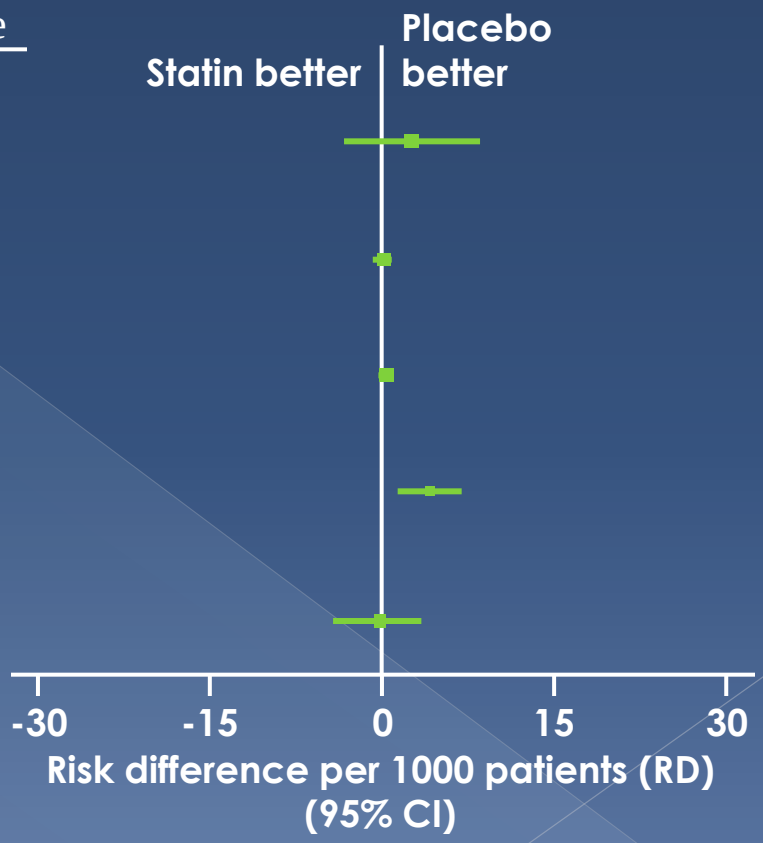
*CHD death, nonfatal non–procedure-related MI, resuscitated cardiac arrest, fatal or nonfatal stroke.

Shepherd J et al. *Diabetes Care*. 2006;29:1220-1226.

Statins are safe but nothing is without risk: Review of 35 statin therapy trials

FDA-approved statin* monotherapy vs placebo (N = 74,102)

Outcome	Statin (%)	Placebo (%)	RD	P value
Myalgias	15.4	18.7	2.7	0.37
CK elevations	0.9	0.4	0.2	0.64
Rhabdomyolysis	0.2	0.1	0.4	0.13
LFT elevation	1.4	1.1	4.2	<0.01
AE discontinuation	5.6	6.1	-0.5	0.80

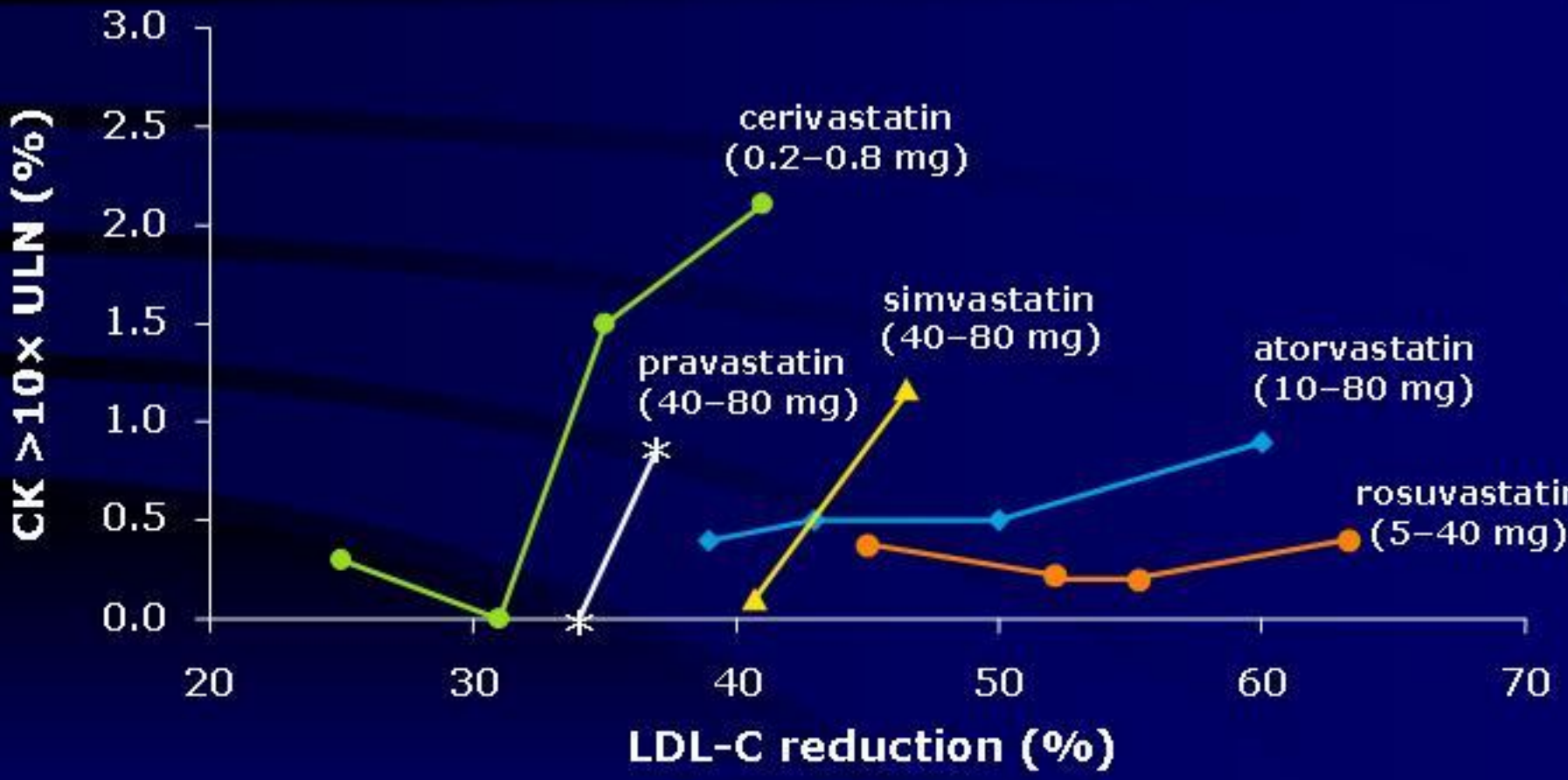


***Atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin, simvastatin**
CK = creatine kinase
AE = adverse events

Kashani A et al. *Circulation*. 2006;114:2788-97.

Rosuvastatin Tolerability and Safety – Muscle Effects

CK >10x ULN: Frequency by LDL-C Reduction



Brewer HB. Am J Cardiol 2003;92(Suppl):23K–29K;
Davidson M, Exp Opin Drug Saf 2004;3(6:547–557)

Fattori predisponenti per miopatia indotta da statine

- Disfunzione renale
- Ipotiroidismo
- Storia familiare di intolleranza alle statine
- Storia di tossicità muscolare con un'altra statina o con un fibrato
- Alcoolismo
- Età superiore a 70
- Situazioni di potenziale incremento delle concentrazioni plasmatiche delle statine
- Uso concomitante di fibrati

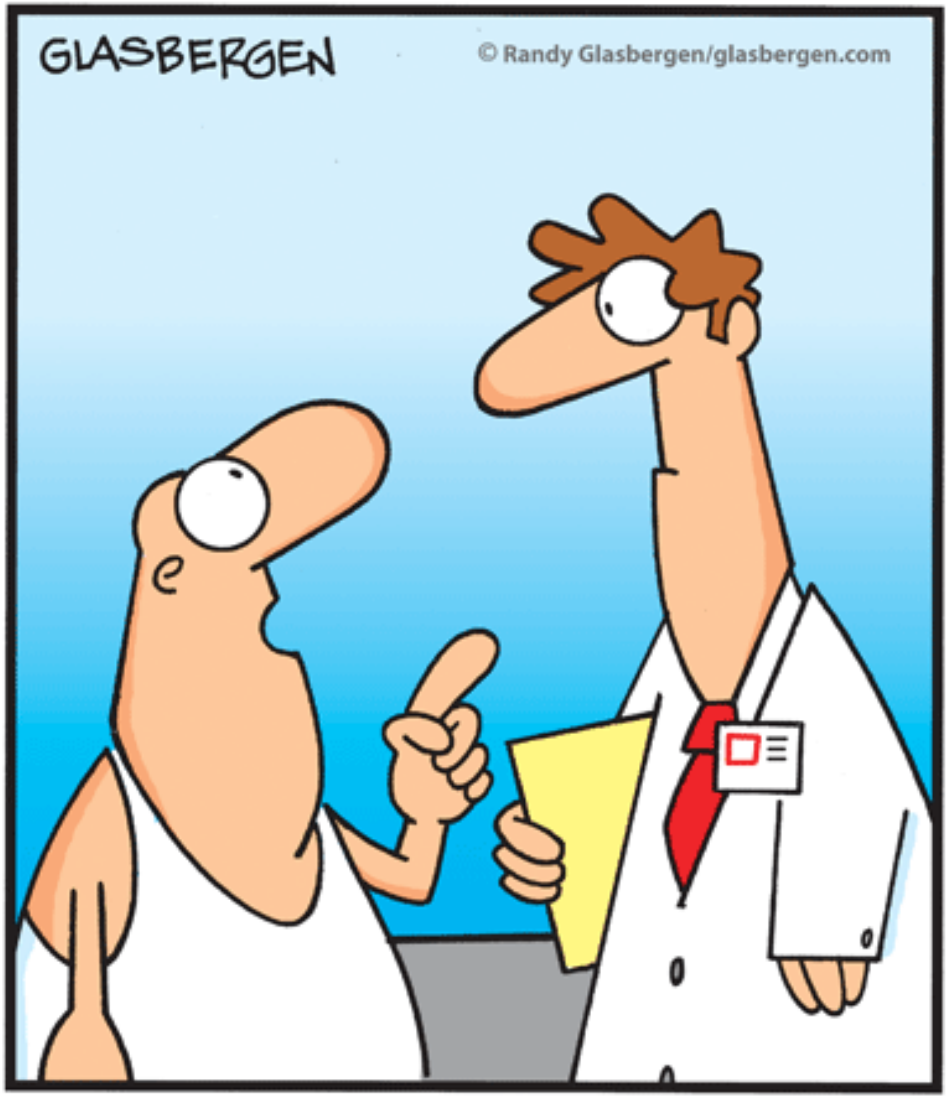
Statin Pearls

- Elevate transaminasi in tr. statinico (sotto il 3X rispetto alla norma), non sono ragione sufficiente per interrompere – sorvegliare attentamente.
- Gli effetti collaterali delle statine sono spesso molecola specifici, non sempre classe specifici.
- Mialgie possono manifestarsi, sotto statine, senza elevazione della CPK. Provare una statina diversa.

Statin Pearls

- La rabdomiolisi è infrequente per valori di CPK inferiori a 10X. Di solito si manifesta in pazienti con comorbidità multiple.
- Può essere inutile controllare in modo sistematico la CPK durante il trattamento. Ricordare che l'esercizio intenso può elevare notevolmente CPK. Secondo alcuni un CPK baseline può essere utile.
- Rabdomiolisi: ? deplezione di mevalonato, farnesolo, geranilgeraniolo, e ubiquinone mitocondriale
- Neuropatia periferica: ? Rischio basso; segnalato nei diabetici

"All people over the age of 40 with diabetes--type 1 or type 2--should be taking statins to reduce their risk of stroke or coronary events" Dr John Betteridge, University College London UK, EASD meeting, Stockholm 2010



IL DIABETE E' AUMENTATO DRAMMATICAMENTE NEGLI ULTIMI 20 ANNI. QUESTO PROVA CHE IL DIABETE E' CAUSATO DAL RISCALDAMENTO GLOBALE!!!

Target secondario: colesterolo non HDL

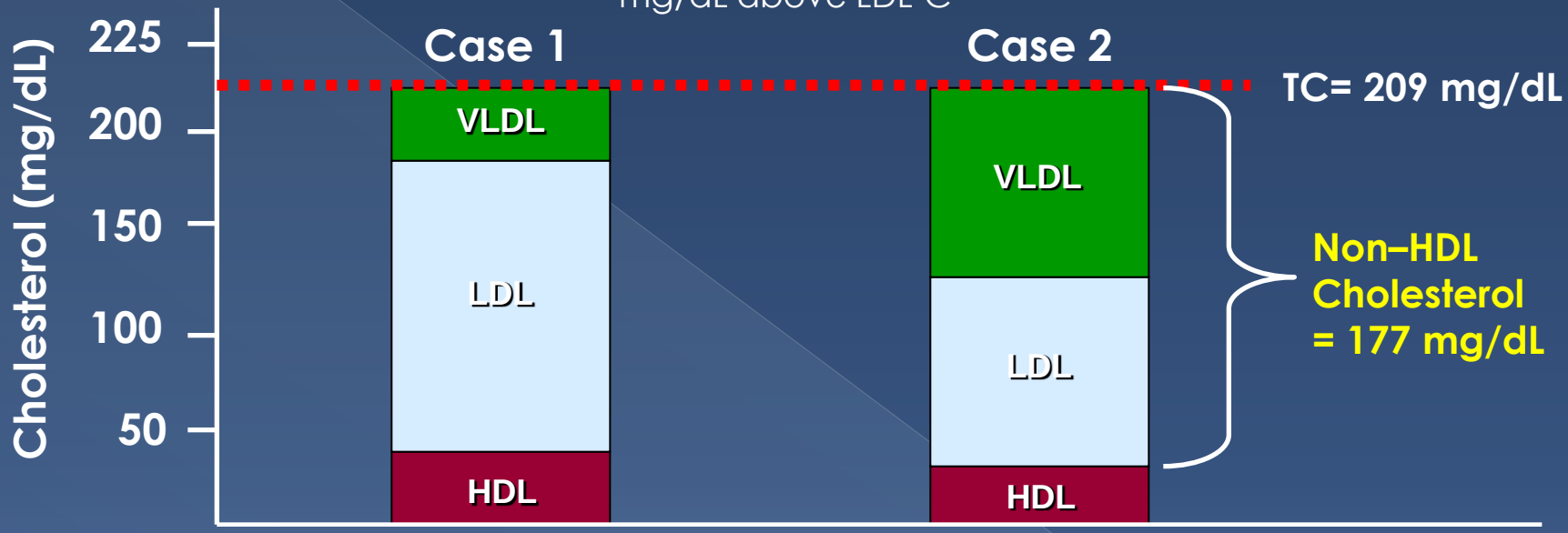
- IL goal è:

GOAL PER IL COLESTEROLO LDL + 30

Quindi, nel diabetico: 130

Why Treat to Non–HDL-C Goals?

Two patient cases with same total cholesterol. Without calculating non–HDL-C, Case 2 might not get treated and therefore may be at risk since non–HDL-C goal should not exceed 30 mg/dL above LDL-C

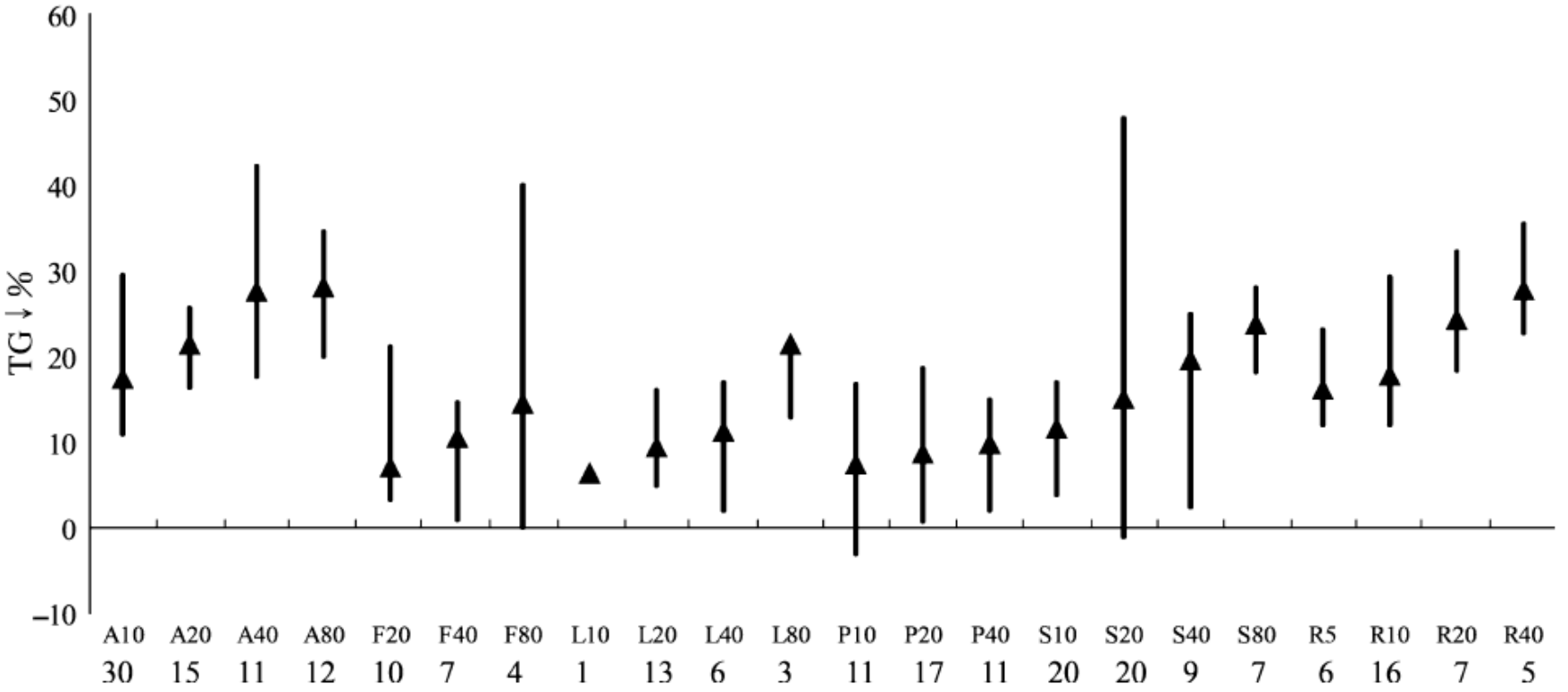


	Case 1	Case 2
TG	120 mg/dL	400 mg/dL
VLDL-C	24 mg/dL	88 mg/dL
LDL-C	145 mg/dL	89 mg/dL
HDL-C	40 mg/dL	32 mg/dL
Non–HDL-C	169 mg/dL	177 mg/dL
TG/HDL-C ratio	3.0	12.5
TC	209 mg/dL	209 mg/dL

Non–HDL-C goal = LDL-C goal + 30

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TC = total cholesterol; TG = triglyceride; VLDL = very low-density lipoprotein

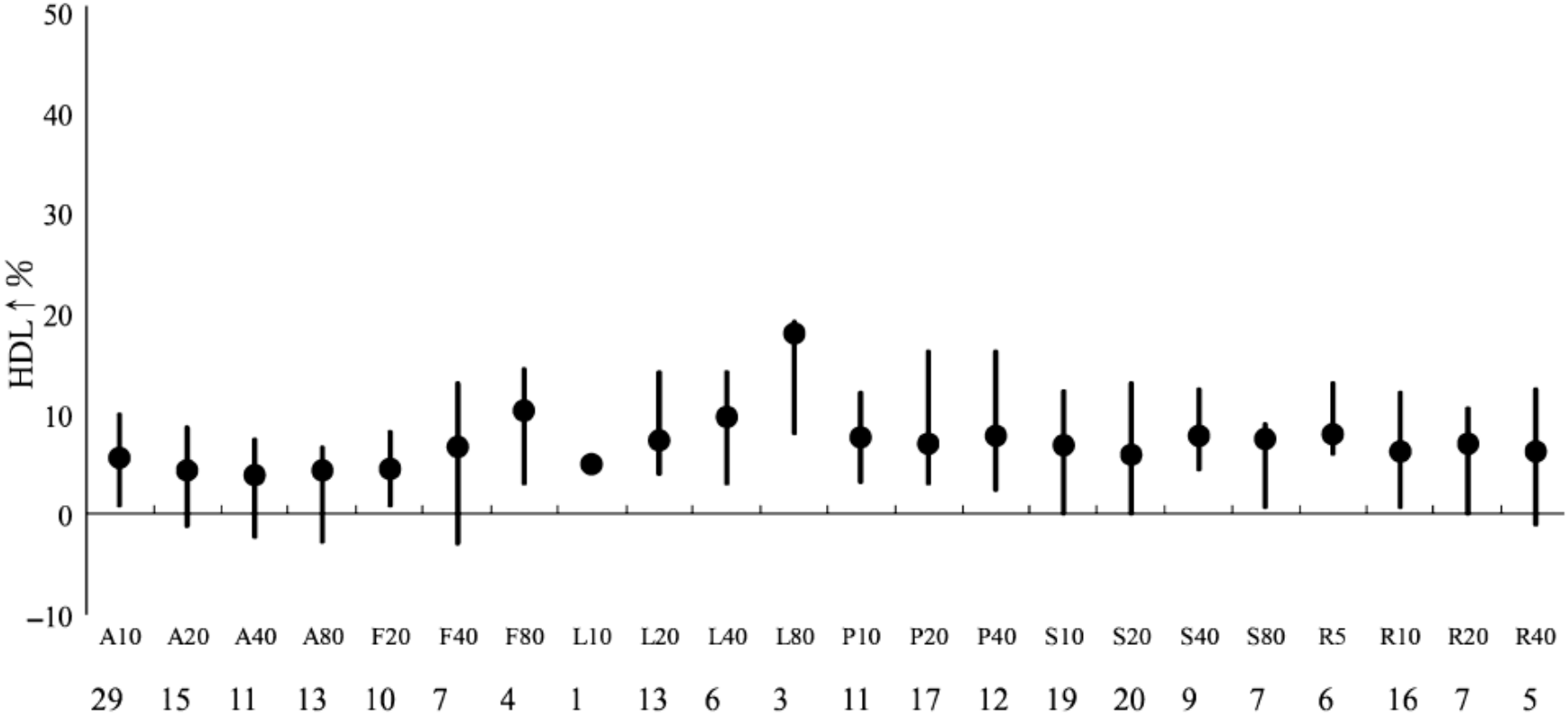
Comparisons of the lipid lowering effect of different statins: TG



→. Comparisons of the lipid lowering effect of different statins. (1) The point estimate indicates the weighted-average of pooled analysis, and the vertical bar shows the range of lipid-lowering effects of the included studies. (2) The horizontal axis is composed of drug labels, indicating the specific statin and dose studied. A, F, L, P, S, and R stand for atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, and rosuvastatin, respectively, whereas the number after the single alphabet represents the dose used. For examples, A10 is atorvastatin 10 mg and S20 is simvastatin 20 mg. Under each drug label is the number of head-to-head comparisons involving the specific dose and statin. To illustrate, the first panel [low-density lipoprotein (LDL)-lowering effect] shows that 31 clinical trials with atorvastatin 10 mg reported the drug could reduce LDL by 28·9–42.

Weng TC, et al. J Clin Pharm Ther 2010;35:139-51

Comparisons of the lipid lowering effect of different statins: HDL



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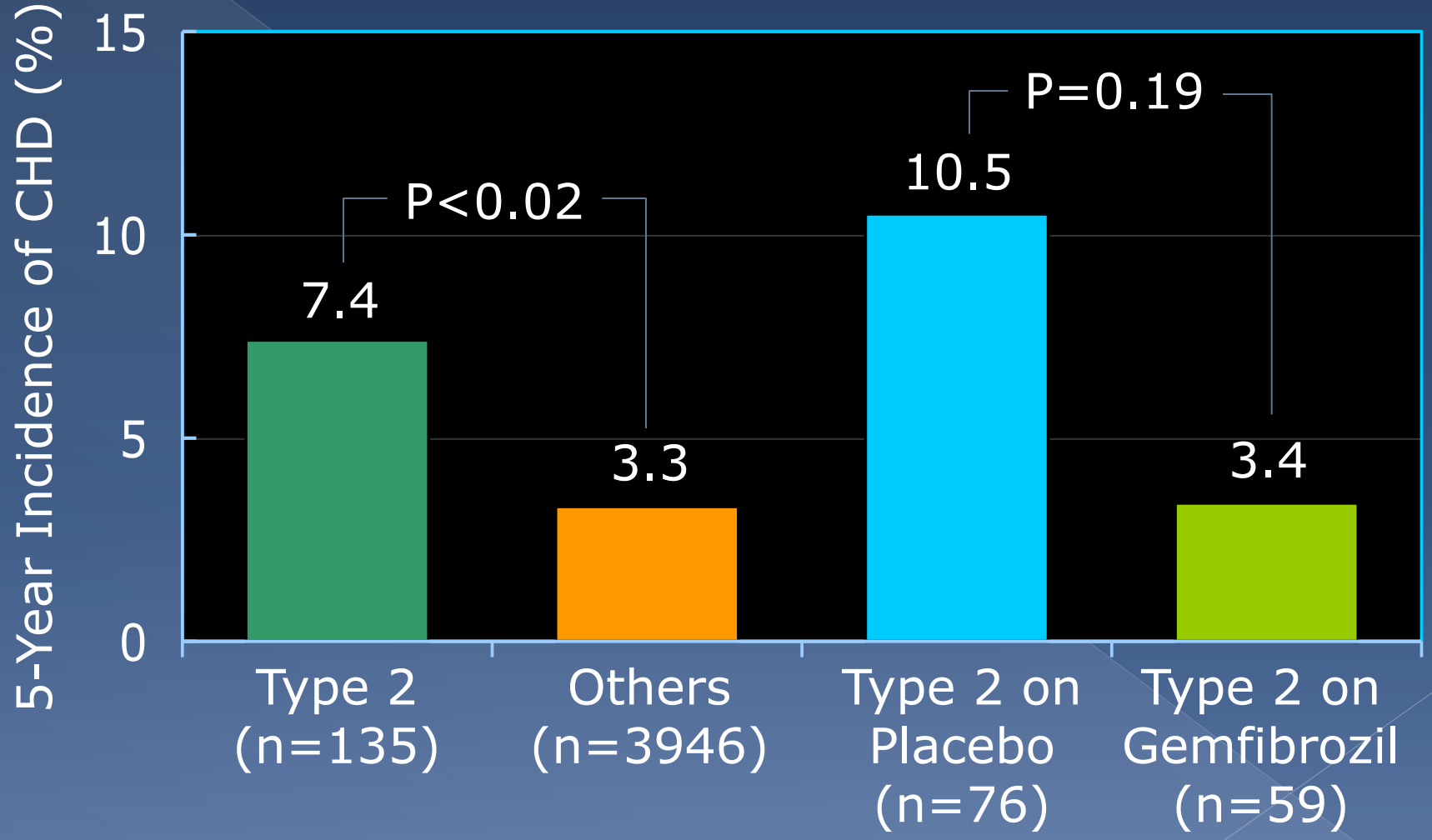
Weng TC, et al. J Clin Pharm Ther 2010;35:139-51

Primary CHD* Prevention in Type 2 Diabetic Patients: *The Helsinki Heart Study*

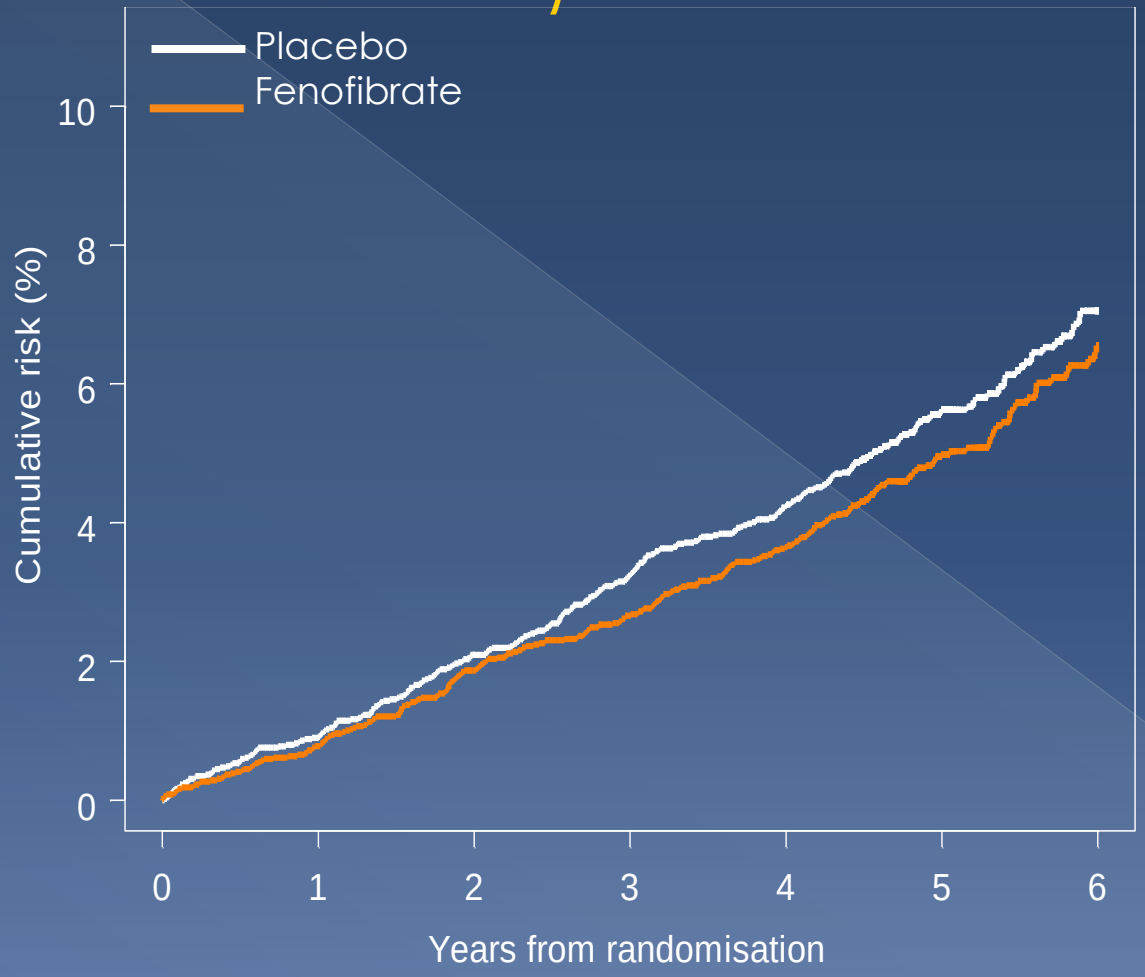


*Myocardial infarction or cardiac death

Adapted from Koskinen P et al. *Diabetes Care* 1992;15:820-825.

FIELD results: primary outcome

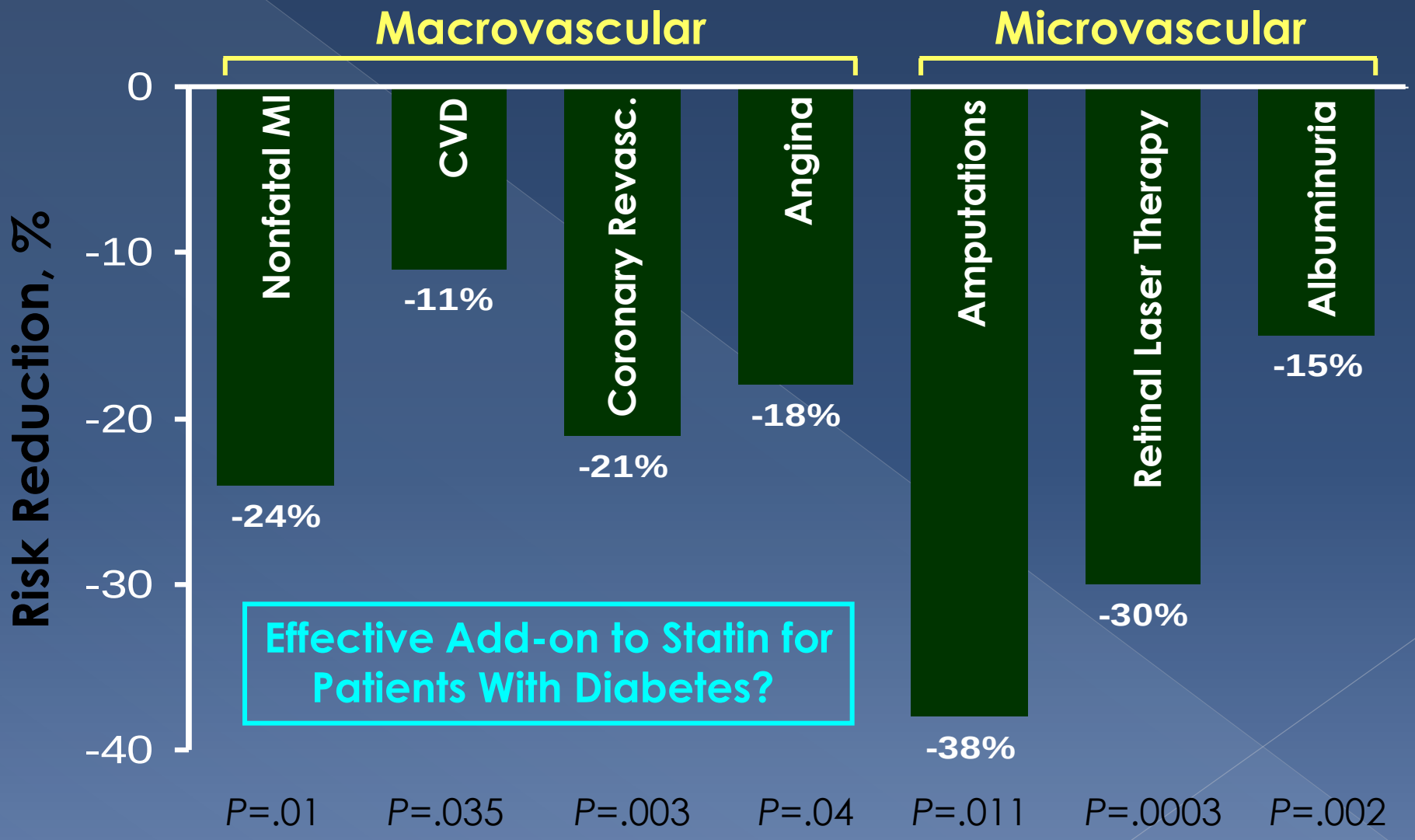
CHD events (CHD death + nonfatal MI)



HR = 0.89
95% CI = 0.75–1.05
P=0.16

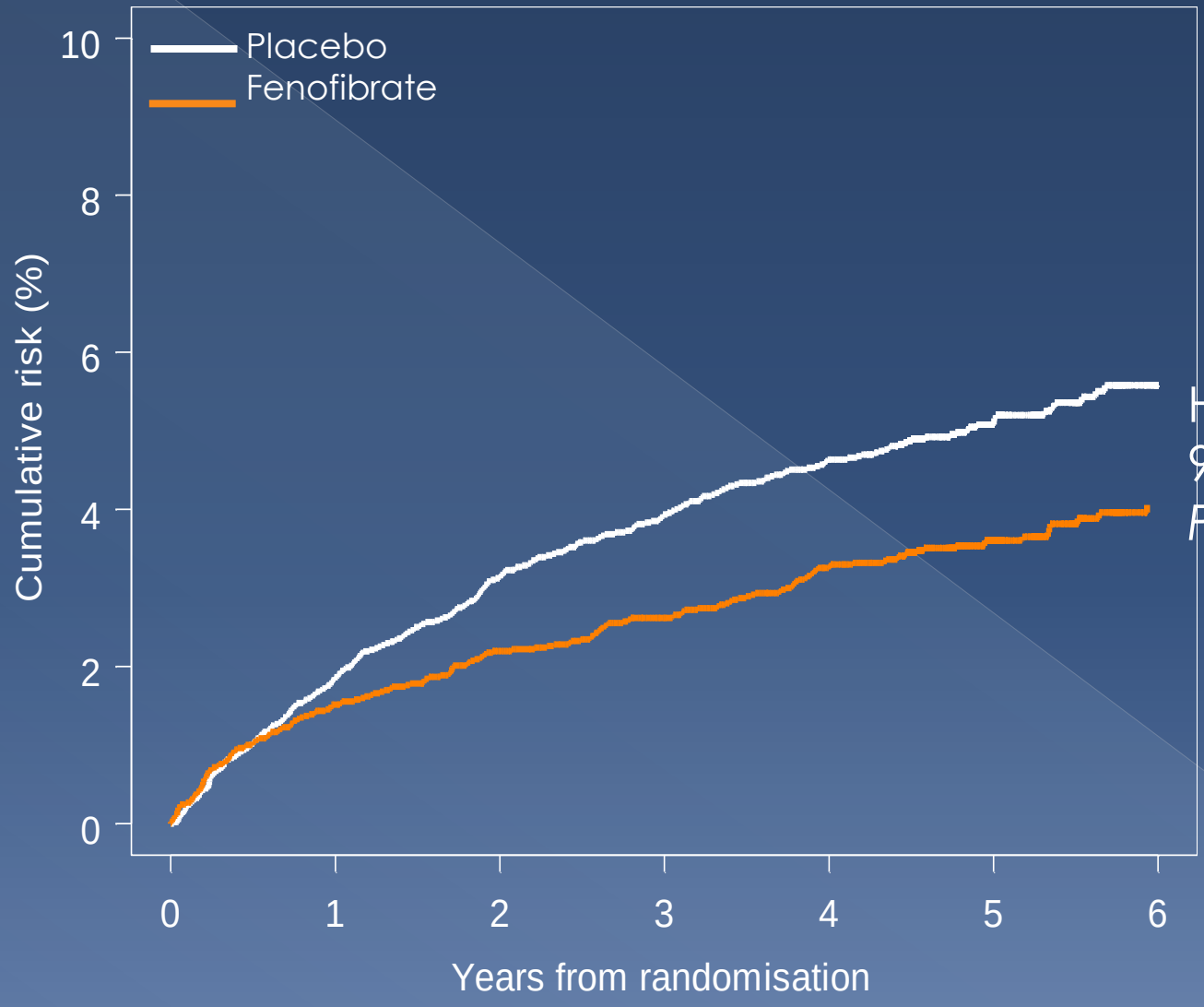
Placebo	4900	4835	4741	4646	4547	2541	837
Fenofibrate	4895	4837	4745	4664	4555	2553	850

FIELD: Fenofibrate Reduces the Risk for Vascular Complications of Diabetes



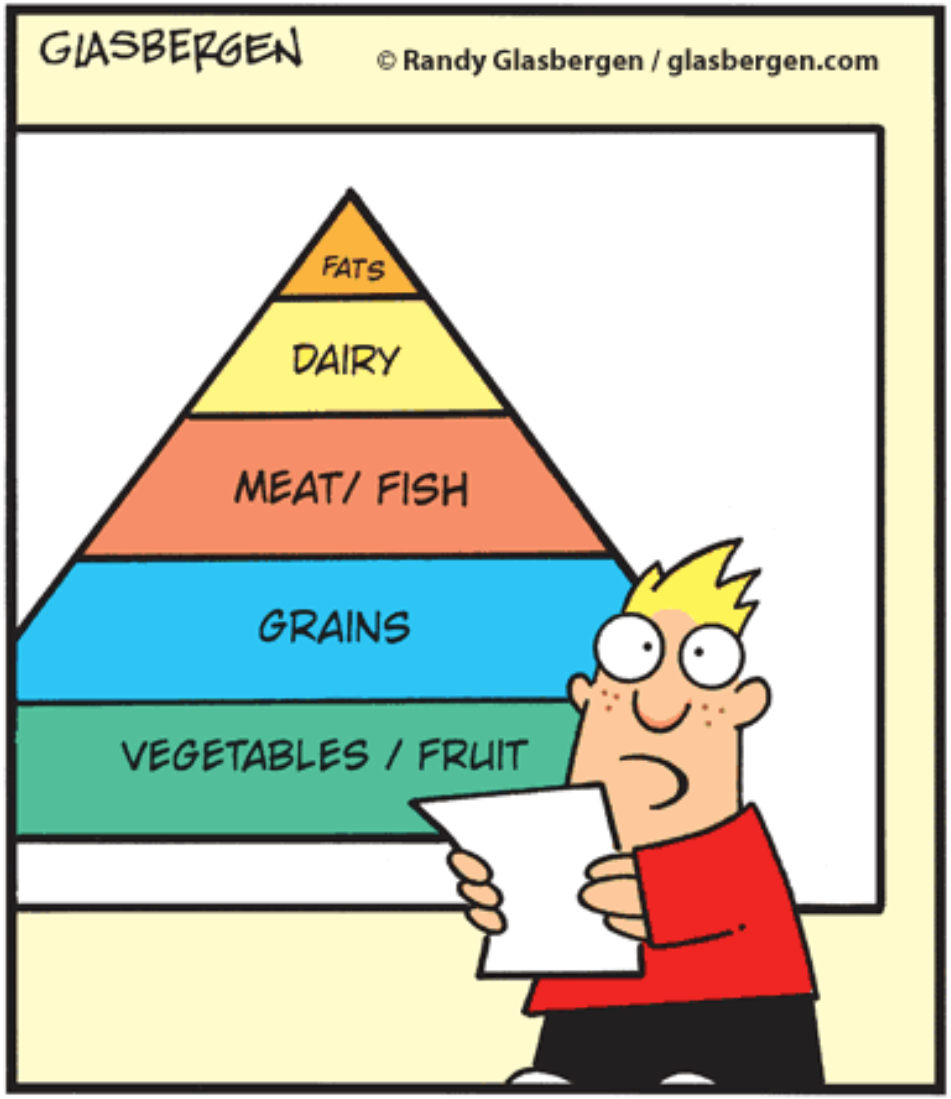
Keech A, et al. *Lancet.* 2005;366(9500):1849-1861.
Keech A. *Atherosclerosis Supplements.* 2006;7:342. Abstract.

Results: retinal laser therapy



HR = 0.70
95% CI = 0.58–0.85
P=0.0003

Placebo	4900	4775	4664	4573	4472	2518	835
Fenofibrate	4895	4792	4701	4618	4502	2529	841



LA PRIMA PIRAMIDE ALIMENTARE E' STATA COSTRUITA NELL'ANTICO EGITTO DA UN FARAONE CHE ODIAVA LE VERDURE COSI' TANTO CHE LE HA SEPPELLITE ALLA BASE!!!

Despite the need beyond LDLc lowering, outcomes data supporting combination therapy still limited

- If targets are not reached on maximally tolerated doses of statins, combination therapy using statins and other lipid-lowering agents may be considered to achieve lipid targets but has not been evaluated in outcome studies for either CVD outcomes or safety. (E)

ADA Standards of Care; Diabetes Care, January 2011

Il braccio lipidi dell' ACCORD trial è stato non incoraggiante rispetto alla terapia di associazione

Effects of Combination Lipid Therapy in Type 2 Diabetes Mellitus

The ACCORD Study Group*

ABSTRACT

BACKGROUND

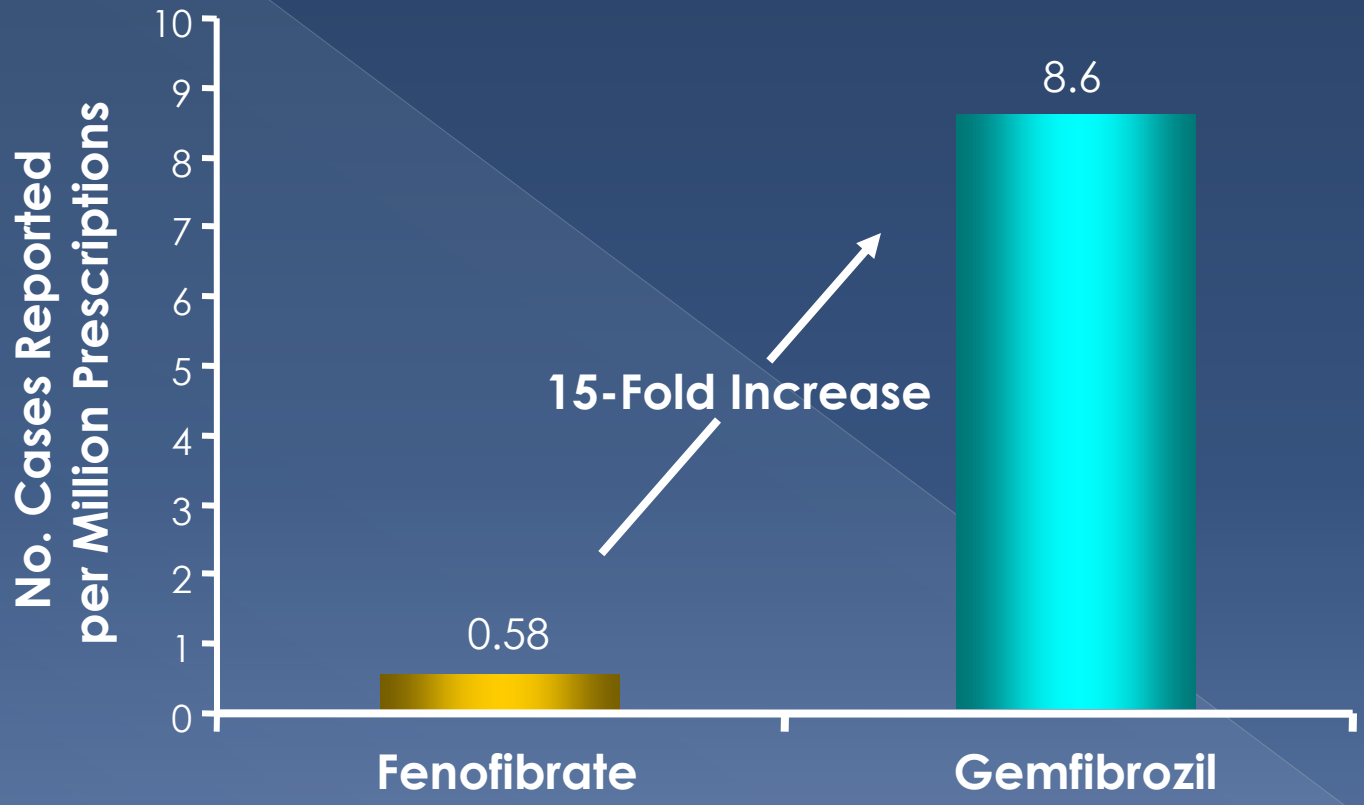
We investigated whether combination therapy with a statin plus a fibrate, as compared with statin monotherapy, would reduce the risk of cardiovascular disease in patients with type 2 diabetes mellitus who were at high risk for cardiovascular disease.

The members of the Writing Committee (Henry N. Ginsberg, M.D., Marshall B. Elam, M.D., Laura C. Lovato, M.S., John R. Crouse III, M.D., Lawrence A. Leiter, M.D., Peter Linz, M.D., William T. Friede-

April 29, 2010 N Engl J Med

Conclusioni: "LA COMBINAZIONE DI FENOFIBRATO E SIMVASTATINA NON HA RIDOTTO L'INCIDENZA DI EVENTI CARDIOVASCOLARI FATALI, IM NON FATALE, STROKE NON FATALE, VS. LA SIMVASTATINA DA SOLA "

Rhabdomyolysis Rate in Statins Combo: Gemfibrozil >> Fenofibrate



*Excludes cases involving cerivastatin

Jones PH, et al. *Am J Cardiol.* 2005;95:120-122.

Niacin vs Fibrates:
for Diabetic Dyslipidemia

Favoring Fibrates

- Better TG lowering
- Reasonable ↓LDL-C and ↑HDL-C
- Good ↓Lp(a) (feno only)
- Ezetimibe combo data
- Some ↓CHD events (mono)
- ↓ Microvasc. dis. (feno)
- Better overall tolerability
  - No flushing
  - No↑glucose levels
  - No↑gout/uric acid
  - No↑PUD
  - Less ↑Hcy

Favoring Niacin

- Better HDL-C raising
- Reasonable ↓LDL-C and TG
- Better ↓Lp(a) (esp vs. gemfib)
- ↓CHD events (mono & combo)
- ↓Total mortality
- Statin combo compatibility (better than gemfib *only*)
- Statin combo tablet (ERNL)
- Some tolerability advantages
  - Fewer GI Sx (N & V)
  - No↑creatinine
  - No↑gallstones

ADA guidelines changed text related to lipoprotein control in 2008:

- Lower triglycerides to <150 mg/dl (1.7 mmol/l) and raise HDL cholesterol to >40 mg/dl (1.0 mmol/l). In women, an HDL goal 10 mg/dl higher (>50 mg/dl) should be considered. (C)

ADA guidelines, 2007

- Triglycerides levels <150 mg/dl (1.7 mmol/l) and HDL cholesterol >40 mg/dl (1.0 mmol/l) in men and >50 mg/dl (1.3 mmol/l) in women are desirable. However, LDL cholesterol–targeted statin therapy remains the preferred strategy. (C)

ADA guidelines, 2008-2011

Anti Diabetic Drugs and Lipids

Anti Diabetic Agents	LDL	HDL	TG	LDL Size
Metformin (Mildly favourable)	↓	↔	↓	↔
Pioglitazone (Very favourable)	↔	↑ ↑	↓ ↓	↑
Rosiglitazone (less favourable)	↑	↑	↓	↑
Sulfonylureas (Unfavourable)	↑	↓	↑	↔
Insulin (Not Atherogenic at all)	↓	↔	↓	↑

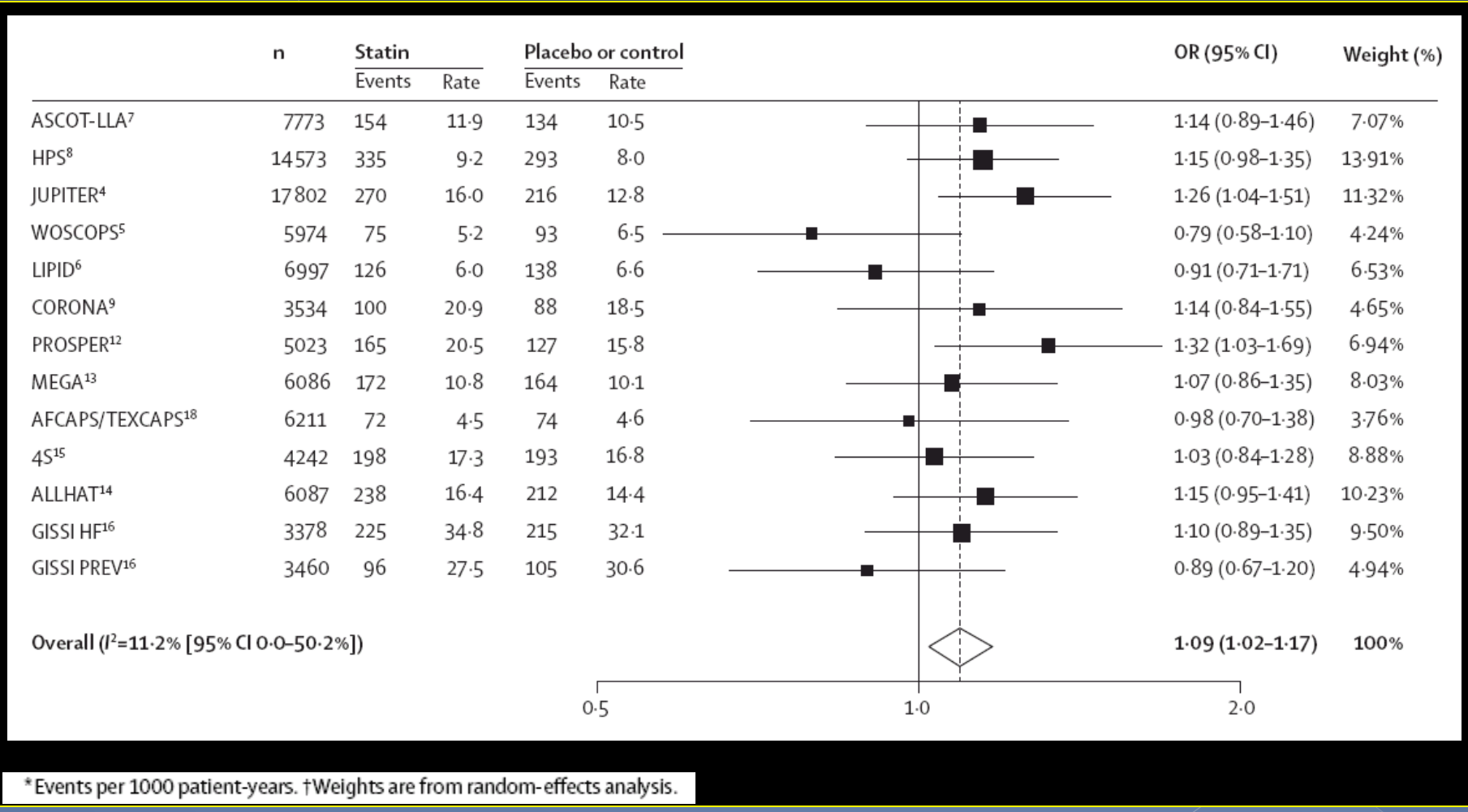
CALENDARIO MAYA:
21 DICEMBRE 2012, LA FINE DEL MONDO!

Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials

Naveed Sattar, David Preiss, Heather M Murray, Paul Welsh, Brendan M Buckley, Anton J M de Craen, Sreenivasa Rao Kondapally Seshasai, John J McMurray, Dilys J Freeman, J Wouter Jukema, Peter W Macfarlane, Chris J Packard, David J Stott, Rudi G Westendorp, James Shepherd, Barry R Davis, Sara L Pressel, Roberto Marchioli, Rosa Maria Marfisi, Aldo P Maggioni, Luigi Tavazzi, Gianni Tognoni, John Kjekshus, Terje R Pedersen, Thomas J Cook, Antonio M Gotto, Michael B Clearfield, John R Downs, Haruo Nakamura, Yasuo Ohashi, Kyoichi Mizuno, Kausik K Ray, Ian Ford

Sattar N, et al. Lancet 2010;375:735-42

Association between statin therapy and incident diabetes in 13 major cardiovascular trials†

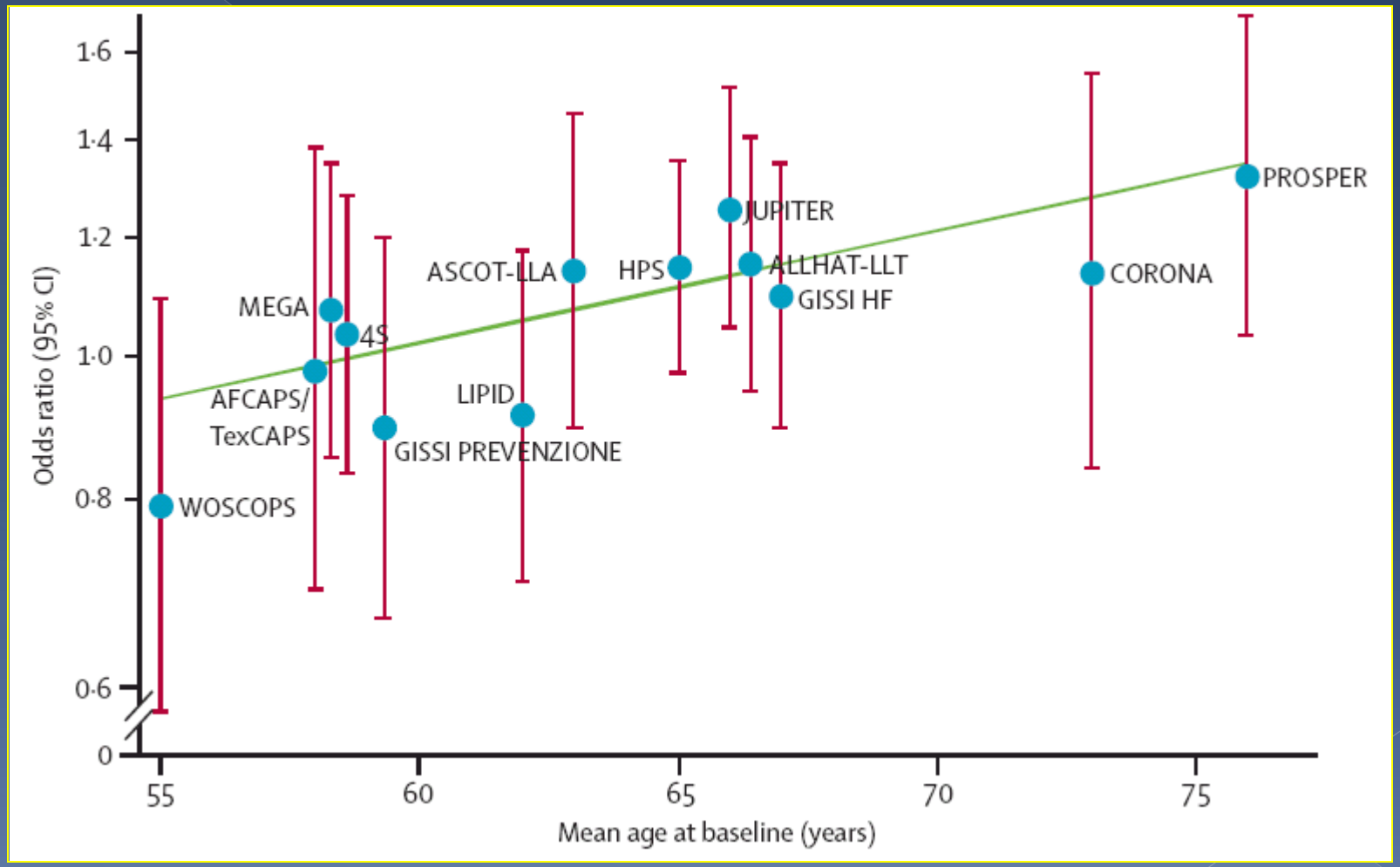


	n	Statin		Placebo or control		OR (95% CI)	Weight (%)
		Events	Rate	Events	Rate		
ASCOT-LLA[7]	7773	154	11·9	134	10·5	1·14 (0·89–1·46)	7·07%
HPS[8]	14573	335	9·2	293	8·0	1·15 (0·98–1·35)	13·91%
JUPITER[4]	17802	270	16·0	216	12·8	1·26 (1·04–1·51)	11·32%
WOSCOPS[5]	5974	75	5·2	93	6·5	0·79 (0·58–1·10)	4·24%
LIPID[6]	6997	126	6·0	138	6·6	0·91 (0·71–1·71)	6·53%
CORONA[9]	3534	100	20·9	88	18·5	1·14 (0·84–1·55)	4·65%
PROSPER[12]	5023	165	20·5	127	15·8	1·32 (1·03–1·69)	6·94%
MEGA[13]	6086	172	10·8	164	10·1	1·07 (0·86–1·35)	8·03%
AFCAPS/TEXCAPS[18]	6211	72	4·5	74	4·6	0·98 (0·70–1·38)	3·76%
4S[15]	4242	198	17·3	193	16·8	1·03 (0·84–1·28)	8·88%
ALLHAT[14]	6087	238	16·4	212	14·4	1·15 (0·95–1·41)	10·23%
GISSI HF[16]	3378	225	34·8	215	32·1	1·10 (0·89–1·35)	9·50%
GISSI PREV[16]	3460	96	27·5	105	30·6	0·89 (0·67–1·20)	4·94%
Overall (I^2=11·2% [95% CI 0·0–50·2%])						**1·09 (1·02–1·17)**	**100%**

*Events per 1000 patient-years. †Weights are from random-effects analysis.

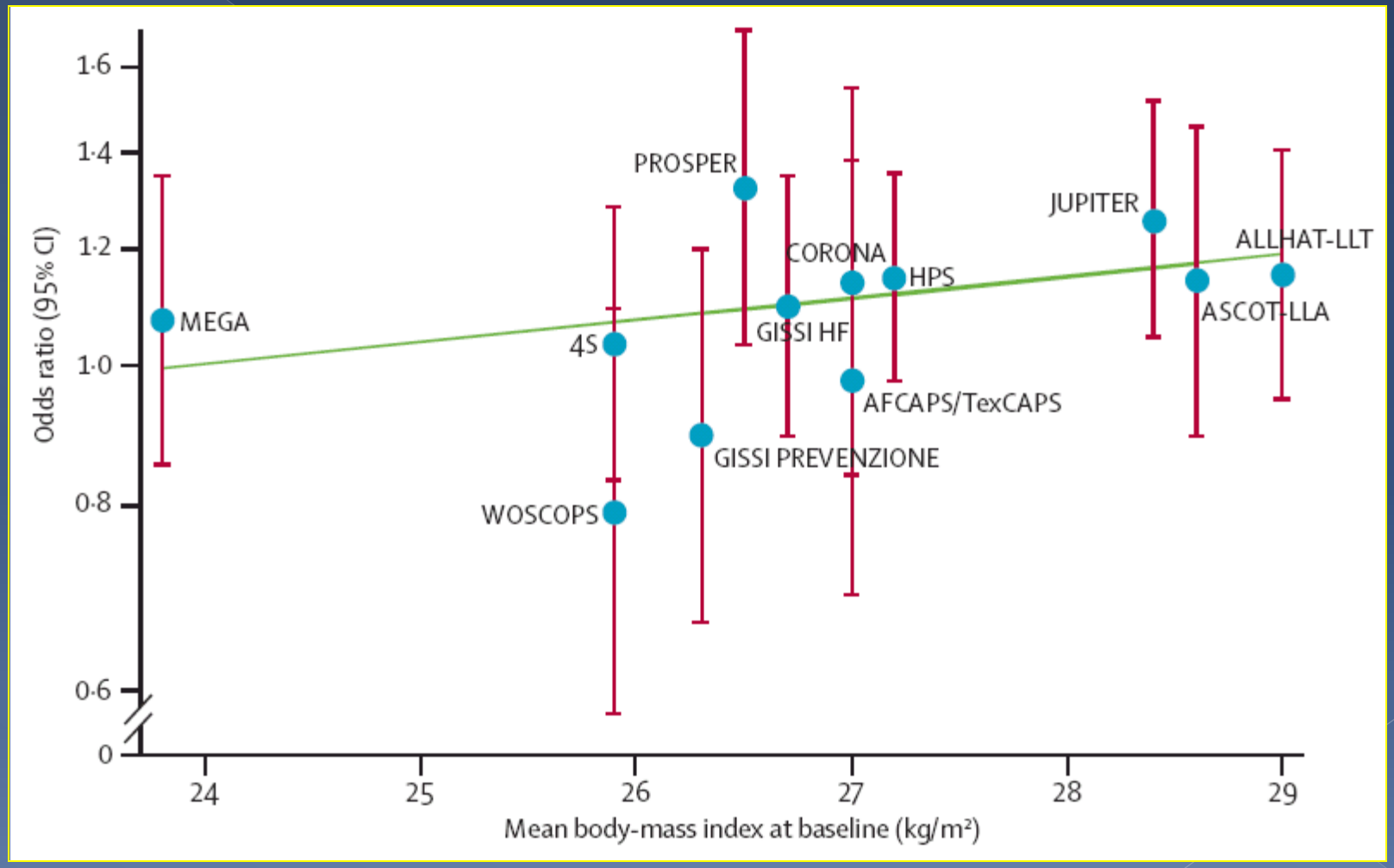
Sattar N, et al. Lancet 2010;375:735-42

Meta-regression of baseline age percentage reduction in LDL-cholesterol concentration for incident diabetes



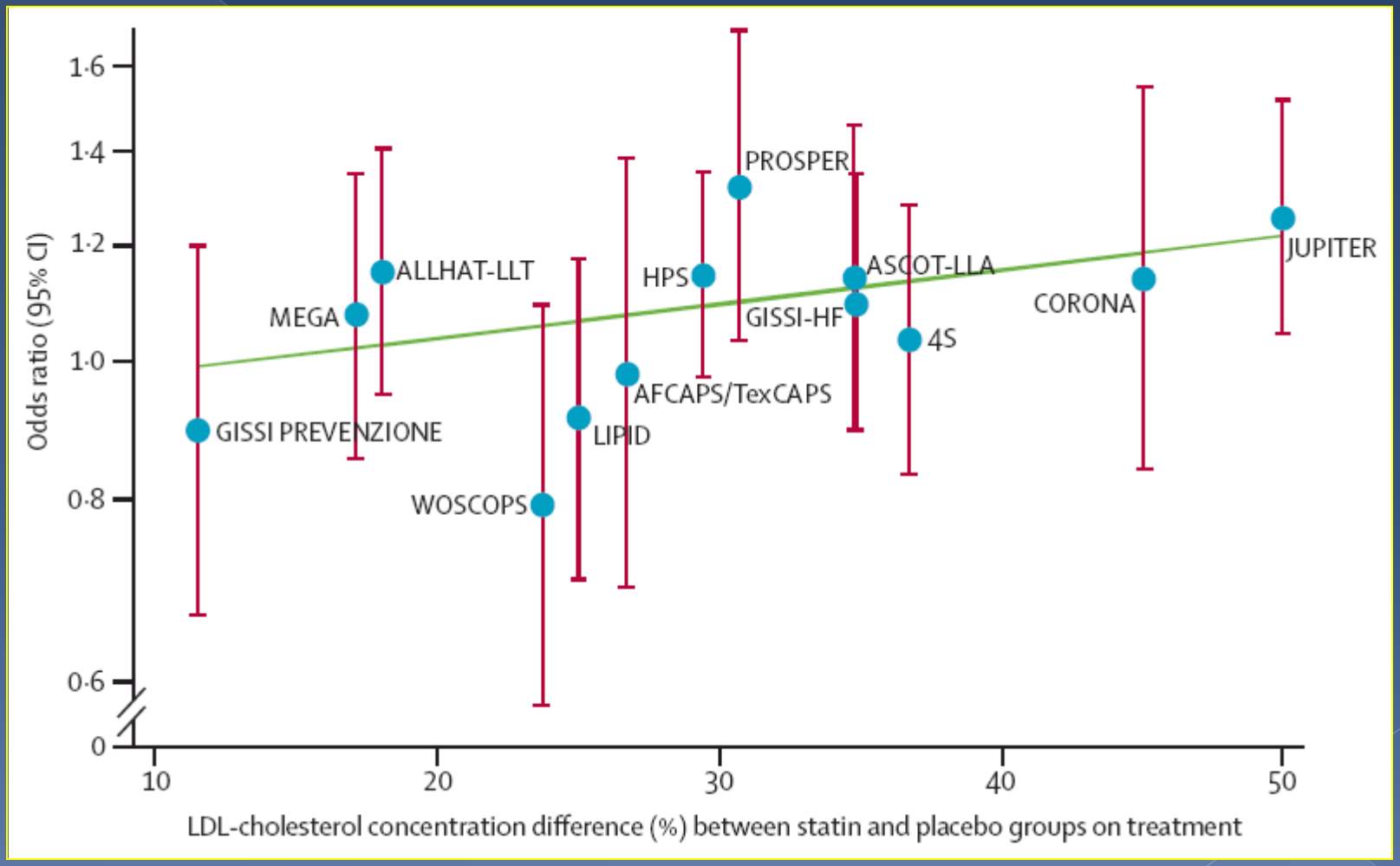
Sattar N, et al. Lancet 2010;375:735-42

Meta-regression of baseline BMI percentage reduction in LDL-cholesterol concentration for incident diabetes

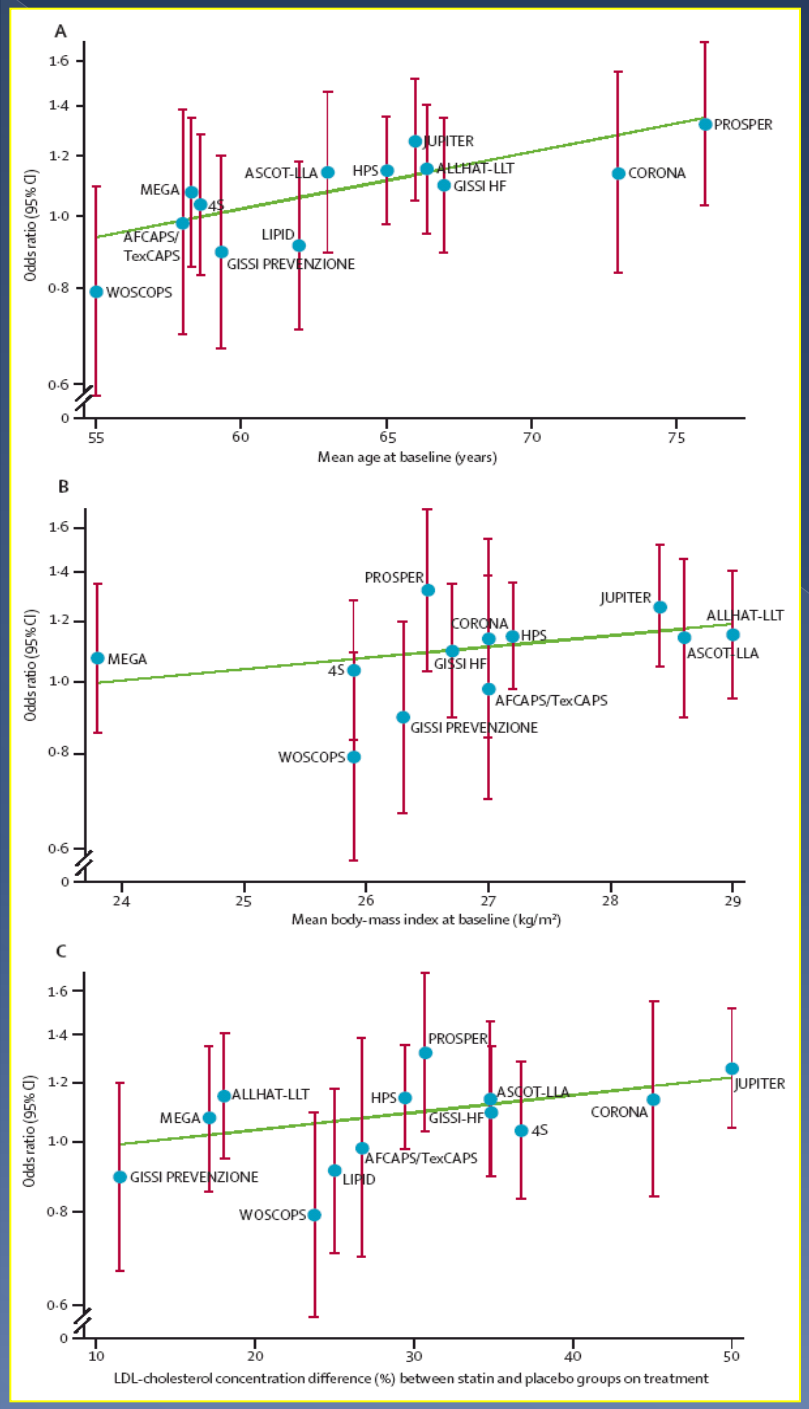


Sattar N, et al. Lancet 2010;375:735-42

Meta-regression of on-treatment percentage reduction in LDL-cholesterol concentration for incident diabetes



Sattar N, et al. Lancet 2010;375:735-42



Meta-regression of (A) baseline age, (B) baseline BMI, and (C) on-treatment percentage reduction in LDL-cholesterol concentration for incident diabetes

Meta-regression
p=0.019 (A),
p=0.177 (B),
p=0.102 (C).

Sattar N, et al. Lancet 2010;375:735-42

CONCLUSIONI

- L'USO DELLE STATINE E' DI DIMOSTRATA EFFICACIA NELLA PREVENZIONE DEGLI EVENTI IN PAZIENTI DIABETICI
- NON C'E' EVIDENZA ASSOLUTA CHE FARMACI IPOLIPIDEMIZZANTI DIVERSI DALLE STATINE RIDUCANO GLI EVENTI
- RECENTEMENTE E' STATO EVIDENZIATO CHE LE STATINE POSSONO INCREMENTARE IL RISCHIO DI INSORGENZA DEL DIABETE


Grazie per l'attenzione